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## Fifteen-year follow-up of quality of life in type 1 diabetes mellitus

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### Abstract

**AIM:** To evaluate metabolic control and health-related quality of life (HRQOL) in a type 1 diabetes mellitus (T1DM) population.

**METHODS:** As part of a prospective cohort study, 283 T1DM patients treated with various insulin treatment modalities including multiple daily injections (MDI) and continuous subcutaneous insulin infusion (CSII) were examined annually. HRQOL was measured using the SF-36 and EuroQol questionnaires. Data regarding HRQOL, glycaemic and metabolic control from baseline and follow-up measures in 2002 and 2010 were

analysed. Linear mixed models were used to calculate estimated values and differences between the three moments in time and the three treatment modalities.

**RESULTS:** Significant changes [mean  $\Delta$  (95%CI)] in body mass index [2.4 kg/m<sup>2</sup> (1.0, 3.8)], systolic blood pressure [-6.4 mmHg (-11.4, -1.3)] and EuroQol-VAS [-7.3 (-11.4, -3.3)] were observed over time. In 2010, 168 patients were lost to follow-up. Regarding mode of therapy, 52 patients remained on MDI, 28 remained on CSII, and 33 patients switched from MDI to CSII during follow-up. Among patients on MDI, HRQOL decreased significantly over time: mental component summary [-9.8 (-16.3, -3.2)], physical component summary [-8.6 (-15.3, -1.8)] and EuroQol-VAS [-8.1 (-14.0, -2.3)],  $P < 0.05$  for all. For patients using CSII, the EuroQol-VAS decreased [-9.6 (-17.5, -1.7)]. None of the changes over time in HRQOL differed significantly with the changes over time within the other treatment groups.

**CONCLUSION:** No differences with respect to metabolic and HRQOL parameters between the various insulin treatment modalities were observed after 15 years of follow-up in T1DM patients.

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**Key words:** Type 1 diabetes mellitus; Health-related quality of life; Glycaemic control; Insulin treatment; Multiple daily injections; Continuous subcutaneous insulin infusion

**Core tip:** The results of this study demonstrate that over a period of 15 years, general health-related quality of life is almost stable among patients with type 1 diabetes mellitus. In addition, no differences with respect to metabolic control and general health-related quality of life were observed among type 1 diabetes mellitus patients treated with different insulin regimens (multiple daily injections or continuous subcutaneous insulin infusion).

van Dijk PR, Logtenberg SJJ, Groenier KH, Keers JC, Bilo HJG, Kleefstra N. Fifteen-year follow-up of quality of life in type 1 diabetes mellitus. *World J Diabetes* 2014; 5(4): 569-576 Available from: URL: <http://www.wjgnet.com/1948-9358/full/v5/i4/569.htm> DOI: <http://dx.doi.org/10.4239/wjd.v5.i4.569>

## INTRODUCTION

Patients with type 1 diabetes mellitus (T1DM) require lifelong daily insulin to compensate for an absolute endogenous insulin shortage. In many patients, it is possible to achieve adequate or even tight glycaemic control and delay the onset and progression of micro- and macrovascular complications with intensive insulin therapy<sup>[1]</sup>. At present, multiple daily injections (MDI) and continuous subcutaneous insulin infusion (CSII) are the most common forms of insulin administration in T1DM.

It is likely that T1DM and its therapy impact health-related quality of life (HRQOL)<sup>[2]</sup>. Previous studies have underlined the importance of this association by revealing a negative association between HRQOL and diabetes prognosis<sup>[3-5]</sup>. In T1DM, a relevant deterioration of HRQOL and glycaemic control during the disease course has been reported<sup>[6,7]</sup>. In contrast, reports have also found no association between duration of diabetes and scores on quality of life scales<sup>[8,9]</sup>. In addition to diabetes duration and clinical and metabolic characteristics, such as body mass index (BMI), the presence of macrovascular complications, hyperglycaemic complaints and personal characteristics influence HRQOL. In addition, insulin treatment with CSII is thought to have a positive effect on HRQOL compared with MDI<sup>[2,10,11]</sup>.

The aim of the present analysis was to assess long-term metabolic control and HRQOL in T1DM patients treated with various therapy modes. Furthermore, we aimed to investigate whether mode of therapy (MDI or CSII) influences long-term clinical and HRQOL parameters in T1DM patients.

## MATERIALS AND METHODS

### Study design and population

The study was designed as a prospective, cohort study to investigate several disease factors, including oxidative stress and HRQOL, in T1DM. The full study design has been published in detail previously<sup>[12]</sup>. In brief, from January 1995 to January 1996, consecutive visiting T1DM patients treated at the diabetes outpatient clinic of the Weezenlanden Hospital (currently Isala), Zwolle, The Netherlands, were invited to participate. T1DM was defined as the initiation of insulin therapy within 6 months after the first signs of diabetes and before the age of 30 years or the absence of C-peptide secretion. In total, 293 patients agreed to participate. The main scope was to assess patients treated with MDI or CSII or patients switching from MDI to CSII during the study period. Patients who switched from CSII to MDI and back ( $n = 3$ ) or

from CSII to continuous intraperitoneal insulin infusion ( $n = 8$ ) or underwent a pancreas and kidney transplantation ( $n = 1$ ) were excluded from analysis.

### Measurement of clinical data and HRQOL

At baseline, a trained physician examined all patients according to a standardised protocol. Data concerning demographics, mode of therapy, height, weight, blood pressure and several laboratory measurements were collected. We adjusted the eGFR MDRD values for differences using the conventional Jaffe creatinine method before 2007 and the isotope-dilution mass spectrometry-traceable enzymatic creatinine method after 2007. HRQOL was assessed annually from 1995 to 2001, and these results were reported previously<sup>[12]</sup>. From 2001 onwards, HRQOL was assessed in 2002 and 2010. HRQOL was assessed using the SF-36 and EuroQoL. The SF-36 is a widely used, self-administered generic questionnaire with 36 items involving 8 subscales: physical functioning, role limitations due to physical problems, bodily pain, general health perception, vitality, social functioning, role limitations due to emotional problems, and mental health. Scale scores range from 0 to 100, and higher scores indicate better HRQOL. In addition, a physical and mental component summary (PCS and MCS) score can be determined<sup>[13]</sup>. The EuroQoL is a generic measure developed by researchers from 5 European countries, including The Netherlands<sup>[14]</sup>. The questionnaire has 2 parts. The first part consists of 5 items covering the areas of mobility, self-care, usual activities, pain or discomfort and anxiety or depression (EQ-5D). Each item has 3 levels: no problems, some problems, or extreme problems. EQ-5D scores were converted to a single index value (ranging from 0 for the worst health state to 1 for the best health state) using a value set specific for the Dutch population<sup>[15]</sup>. The second part consists of a visual analogue scale (VAS) from which a single overall score for self-rated health status can be elicited ranging from 0 to 100 (EQ-VAS).

### Ethical considerations

The study was performed in accordance with the Declaration of Helsinki. Informed consent was obtained from all patients, and the protocol was approved by the local medical ethics committee.

### Statistical analysis

All analyses were performed using SPSS version 18.0 (SPSS, Inc., Chicago, IL, United States). A (two-sided) *P*-value of less than 0.05 was considered statistically significant. Q-Q plots were used to determine whether the tested variable had a normal distribution. Where appropriate, paired parametric and non-parametric tests were used to compare outcomes between baseline and follow-up measurements. Linear mixed models with Bonferroni correction were used to calculate estimated values and test differences among the 3 moments in time (1995, 2002 and 2010) and between the 3 treatment modalities

Table 1 Baseline characteristics (including health-related quality of life parameters) for all patients included and for patients who did an did not completed long term follow-up, categorized per treatment modality

Clinical characteristics	All enrolled patients ( <i>n</i> = 281)	Patients who completed follow-up until 2002 (A) ( <i>n</i> = 201)	Patients who completed follow-up until 2010 (B) ( <i>n</i> = 113)	Patients who did not completed follow-up until 2010 (C) ( <i>n</i> = 168)	MDI ( <i>n</i> = 52)	From MDI to CSII ( <i>n</i> = 33)	CSII ( <i>n</i> = 28)	<i>P</i> -value (A vs B)	<i>P</i> -value (B vs C)
Age (yr)	37.2 (28.5, 45.0)	36.7 (29.0, 43.4)	37.1 (29.4, 43.0)	37.1 (27.4, 45.8)	37.6 (31.1, 43.1)	37.8 (29.8, 43.0)	34.1 (28.5, 43.9)	0.70	0.96
Sex (male)	154 (54.8)	117 (57.4)	72 (63.7)	82 (48.8)	37 (71.2)	25 (75.8)	10 (35.7)	0.25	0.01
Diabetes duration (yr)	15.0 (9.0, 23.0)	14.1 (8.7, 21.8)	13.4 (5.5, 21.2)	17.0 (10.9, 24.0)	12.3 (4.80, 21.2)	11.0 (3.70, 20.2)	17.0 (11.9, 25.9)	0.47	0.01
BMI (kg/m <sup>2</sup> )	24.4 (22.4, 26.6)	24.5 (22.6, 26.6)	24.7 (22.5, 26.7)	24.3 (22.3, 26.6)	24.8 (22.6, 27.1)	24.1 (22.6, 25.9)	24.8 (22.4, 26.9)	0.90	0.55
Systolic BP (mmHg)	139.1 (± 18.4)	137.8 (± 17.1)	137.6 (± 17.2)	140.0 (± 19.2)	140.8 (± 20.0)	131.8 (± 17.2)	138.5 (± 13.7)	0.97	0.27
HbA <sub>1c</sub> (%)	8.2 (± 1.8)	7.6 (± 1.0)	7.9 (± 1.8)	8.5 (± 1.7)	7.6 (± 1.8)	8.0 (± 1.7)	8.4 (± 1.8)	0.65	0.01
Total cholesterol (mmol/L)	5.0 (± 1.0)	4.9 (± 0.9)	4.8 (± 0.9)	5.1 (± 1.1)	4.9 (± 1.0)	4.5 (± 1.0)	5.1 (± 0.7)	0.74	0.04
eGFR (MDRD; mL/min per 1.73 m <sup>2</sup> )	86.8 (± 23.0)	87.8 (± 21.8)	88.8 (± 15.8)	85.4 (± 26.8)	90.4 (± 15.0)	91.1 (± 15.4)	83.3 (± 16.8)	0.67	0.27
Smoking (yes)	54 (19.2)	54 (26.5)	31 (27.4)	23 (13.6)	17 (32.7)	6 (18.2)	8 (28.6)	1.00	0.95
Nephropathy (present)	55 (19.6)	34 (16.7)	17 (15.0)	38 (22.6)	10 (19.2)	3 (9.1)	4 (14.3)	0.72	0.12
Neuropathy (present)	76 (27.0)	27 (13.2)	12 (10.6)	64 (38.1)	8 (15.4)	3 (9.1)	1 (3.6)	0.53	0.01
Retinopathy (present)	96 (34.2)	64 (31.4)	32 (28.3)	64 (38.1)	14 (26.9)	7 (21.2)	11 (39.3)	0.59	0.09
Macrovascular complications (present)	2 (0.7)	2 (1.0)	1 (0.9)	1 (0.6)	1 (1.9)	0 (0)	0 (0)	0.94	0.78
Albuminuria (present)	48 (17.1)	29 (14.2)	16 (14.2)	32 (19.0)	9 (17.3)	3 (9.1)	4 (14.3)	0.99	0.30
ACEi	17 (6.0)	16 (7.8)	8 (7.1)	9 (5.4)	4 (7.7)	2 (6.1)	2 (7.1)	0.75	0.39
HRQOL parameters									
SF-36									
MCS	83.5 (71.4, 89.1)	84.8 (74.6, 89.6)	85.3 (77.0, 90.6)	80.2 (65.99, 88.0)	88.1 (82.8, 92.7)	85.2 (73.4, 89.6)	78.0 (68.6, 89.1)	0.20	0.01
PCS	86.8 (75.3, 92.8)	87.8 (79.1, 92.9)	88.7 (79.5, 93.7)	83.6 (70.7, 91.2)	91.4 (86.4, 94.6)	88.3 (74.4, 93.3)	87.4 (74.3, 91.2)	0.24	0.01
EuroQol									
EuroQol-5D	1.00 (0.81, 1.00)	1.00 (0.84, 1.00)	1.00 (0.84, 1.00)	0.95 (0.78, 1.00)	1.00 (0.89, 1.00)	1.00 (0.84, 1.00)	1.00 (0.84, 1.00)	0.39	0.01
EuroQol-VAS	85.0 (70.0, 91.0)	85.0 (75.0, 92.0)	85.0 (80.0, 95.0)	80.0 (70.0, 90.0)	87.5 (80.0, 95.0)	85.0 (70.0, 90.5)	84.5 (70.8, 95.0)	0.45	0.02

Data are mean (± SD), median (interquartile range) or *n* (%). *P*-values are based on unpaired student *T*-, Mann-Whitney *U*- or  $\chi^2$ -tests. HRQOL: Health-related quality of life; BP: Blood pressure; eGFR: Estimated glomerular filtration rate; MDI: Multiple daily injections; CSII: Continuous subcutaneous insulin infusion; MDRD: Modification of diet in renal disease; MCS: Mental component summary; ACEi: Angiotensin-converting enzyme inhibitors.

for patients completing follow-up. The observed and estimated values of the clinical and HRQOL parameters were calculated using linear mixed models and reported.

## RESULTS

### Patients

Of the 281 patients who entered the study, 201 (71.5%) and 113 (40.2%) were available for follow-up measurements of HRQOL in 2002 and 2010, respectively.

The reasons for dropping out of the study were unknown (*n* = 32), moving out of the area or referral to another physician (*n* = 48), death (*n* = 21), lack of interest (*n* = 7) and incorrect diagnosis of T1DM (*n* = 2). Compared with patients who completed follow-up, individuals who eventually dropped out were more often women or patients with increased diabetes duration, a higher HbA<sub>1c</sub> and total cholesterol, a lower eGFR and more often neuropathy at baseline (*P* < 0.05). In addition, these patients displayed lower HRQOL scores at baseline (*P* < 0.05, Table 1). No differences in baseline characteristics were observed between patients with follow-up until 2002 *vs* 2010.



Table 2 Observed clinical parameters and health-related quality of life at long-term follow-up

Clinical characteristics	1995			2002			2010				
	All ( <i>n</i> = 281)	MDI ( <i>n</i> = 209)	CSII ( <i>n</i> = 72)	All ( <i>n</i> = 201)	MDI ( <i>n</i> = 110)	CSII ( <i>n</i> = 91)	All ( <i>n</i> = 113)	MDI ( <i>n</i> = 52)	From MDI to CSII ( <i>n</i> = 33)	CSII ( <i>n</i> = 28)	CSII total ( <i>n</i> = 61)
BMI (kg/m <sup>2</sup> )	24.4 (22.4, 26.6)	24.7 (22.6, 26.9)	23.8 (22.2, 26.0)	25.5 (23.4, 28.4)	25.4 (23.2, 27.8)	25.6 (23.5, 28.7)	24.7 (22.5, 26.7)	25.6 (24.0, 30.2)	26.8 (24.6, 28.8)	25.4 (22.8, 29.3)	26.6 (24.2, 29.0)
Systolic BP (mmHg)	139.1 (± 18.4)	138.9 (± 19.1)	139.5 (± 16.6)	130.5 (± 17.6)	132.5 (± 18.0)	127.8 (± 17.0)	137.6 (± 17.2)	131.9 (± 13.8)	129.4 (± 12.9)	131.1 (± 12.8)	130.2 (± 12.8)
HbA <sub>1c</sub> (mmol/mol)	8.2 (± 1.8)	8.2 (± 1.8)	8.3 (± 1.8)	7.6 (± 1.0)	7.7 (± 1.0)	7.4 (± 1.0)	7.9 (± 1.8)	7.4 (± 1.0)	7.6 (± 0.81)	7.6 (± 0.9)	7.6 (± 0.9)
Total cholesterol (mmol/L)	5.0 (± 1.0)	5.0 (± 1.0)	5.0 (± 1.0)	4.6 (± 0.9)	4.6 (± 0.9)	4.6 (± 1.0)	4.8 (± 0.9)	4.9 (± 0.9)	4.9 (± 0.8)	4.8 (± 0.6)	6.0 (± 0.9)
eGFR (MDRD; mL/min per 1.73 m <sup>2</sup> )	86.8 (± 23.0)	89.0 (± 24.6)	80.5 (± 16.2)	87.8 (± 21.8)	81.5 (± 24.7)	80.8 (± 15.0)	88.8 (± 15.8)	91.0 (± 21.1)	92.2 (± 21.7)	92.8 (± 18.7)	92.5 (± 20.2)
SF-36											
Subscales											
Physical functioning	95.0	95.0	95.0	95.0	95.0	95.0	95.0	95.0	95.0	95.0	95.0
Social functioning	(90.0, 100.0)	(90.0, 100.0)	(76.3, 98.8)	(90.0, 100.0)	(95.0, 100.0)	(90.0, 100.0)	(87.5, 100.0)	(85.0, 100.0)	(85.0, 100.0)	(90.0, 100.0)	(90.0, 100.0)
Role limitations-physical	100.0	100.0	87.5	100.0	100.0	100.0	87.5	93.8	87.5	87.5	87.5
Role limitations-emotional	(75.0, 100.0)	(87.5, 100.0)	(62.5, 100.0)	(87.5, 100.0)	(87.5, 100.0)	(75.0, 100.0)	(75.0, 100.0)	(75.0, 100.0)	(87.5, 100.0)	(65.6, 100.0)	(75.0, 100.0)
Mental health	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0
Vitality	(75.0, 100.0)	(100.0, 100.0)	(50.0, 100.0)	(100.0, 100.0)	(100.0, 100.0)	(68.8, 100.0)	(75.0, 100.0)	(100.0, 100.0)	(75.0, 100.0)	(56.3, 100.0)	(75.0, 100.0)
Bodily pain	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0
General Health	(100.0, 100.0)	(100.0, 100.0)	(33.3, 100.0)	(100.0, 100.0)	(100.0, 100.0)	(66.7, 100.0)	(100.0, 100.0)	(100.0, 100.0)	(100.0, 100.0)	(100.0, 100.0)	(100.0, 100.0)
Component scores	80.0 (68.0, 88.0)	84.0 (72.0, 92.0)	74.0 (60.0, 84.0)	84.0 (72.0, 88.0)	84.0 (76.0, 92.0)	76.0 (68.0, 84.0)	84.0 (76.0, 90.0)	88.0 (80.0, 92.0)	84.0 (72.0, 88.0)	84.0 (73.0, 88.0)	84.0 (72.0, 88.0)
MCS	70.0 (55.0, 80.0)	75.0 (60.0, 85.0)	60.0 (41.3, 80.0)	70.0 (60.0, 80.0)	75.0 (60.0, 85.0)	65.0 (53.8, 80.0)	70.0 (55.0, 80.0)	72.5 (55.0, 80.0)	70.0 (57.5, 80.0)	62.5 (55.0, 78.8)	65.0 (65.0, 80.0)
PCS	100.0 (74.0, 100.0)	100.0 (84.0, 100.0)	84.0 (62.0, 100.0)	100.0 (84.0, 100.0)	100.0 (84.0, 100.0)	100.0 (74.0, 100.0)	100.0 (79.6, 100.0)	100.0 (79.6, 100.0)	89.8 (87.8, 100.0)	89.8 (79.6, 100.0)	89.8 (83.7, 100.0)
EuroQol	72.0 (57.0, 87.0)	72.0 (62.0, 87.0)	67.0 (47.0, 82.0)	72.0 (62.0, 87.0)	77.0 (62.0, 87.0)	72.0 (57.0, 87.0)	65.0 (50.0, 75.0)	65.0 (50.0, 75.0)	65.0 (55.0, 75.0)	65.0 (45.0, 75.0)	65.0 (52.5, 75.0)
EuroQol-5D	83.5 (71.4, 89.1)	84.3 (75.2, 89.9)	75.1 (52.5, 87.2)	80.9 (66.2, 87.7)	80.5 (67.3, 87.1)	80.8 (63.2, 88.1)	85.3 (77.0, 90.6)	83.0 (67.0, 88.9)	80.9 (74.4, 86.2)	78.8 (66.5, 87.5)	80.8 (68.0, 86.5)
EuroQol-VAS	86.8 (75.3, 92.8)	87.8 (79.3, 92.9)	79.1 (57.8, 89.1)	83.5 (70.5, 90.1)	83.5 (73.0, 91.2)	84.0 (68.8, 89.3)	88.7 (79.5, 93.7)	84.9 (75.8, 90.8)	86.3 (74.9, 90.0)	81.9 (68.2, 89.6)	82.9 (74.8, 89.9)
EuroQol	1.00 (0.81, 1.00)	1.00 (0.82, 1.00)	0.84 (0.77, 1.00)	1.00 (0.81, 1.00)	1.00 (0.80, 1.00)	0.95 (0.81, 1.00)	1.00 (0.84, 1.00)	1.00 (0.89, 1.00)	1.00 (0.84, 1.00)	1.00 (0.84, 1.00)	1.00 (0.84, 1.00)
EuroQol-VAS	85.0 (70.0, 91.0)	85.0 (75.0, 91.0)	80.0 (70.0, 93.8)	75.0 (70.0, 85.0)	75.0 (68.8, 85.0)	80.0 (70.0, 86.0)	85.0 (80.0, 95.0)	80.0 (70.0, 90.0)	80.0 (70.0, 85.0)	75.0 (80.0, 85.0)	75.0 (70.0, 85.0)

Data are presented as the mean (SD), *n* (%) or median (interquartile range). BMI: Body mass index; eGFR: Estimated glomerular filtration rate; MDI: Multiple daily injections; CSII: Continuous subcutaneous insulin infusion; MDRD: Modification of diet in renal disease; MCS: Mental component summary; PCS: Physical component summary.

### Therapy mode

Eighty patients remained on the initial treatment mode throughout the follow-up period; 52 were on MDI, and 28 were on CSII. During the follow-up period, 62 patients switched from MDI to CSII, and 33 of these patients completed follow-up. For these patients, the median time between the start of the study and switch in therapy mode was 8.5 years (IQR 4.6). Baseline characteristics of the different treatment groups are presented in Table 1.

### Long term follow-up-clinical parameters

In total, 59 macrovascular complications occurred during follow-up. The number of patients completing follow-up until 2010 and experiencing a macrovascular complication was 16 (14.2%). Eight of these patients were on MDI; 5 were on CSII during the complete follow-up period, and 3 switched from MDI to CSII.

The observed course of clinical parameters, categorised per treatment modality, is presented in Table 2. The estimated clinical parameters using linear mixed models are

**Table 3** Estimated changes in clinical parameters during follow-up

Clinical characteristics	1995 (A)	2002 (B)	Difference (B-A)	P-value	2010 (C)	Difference (C-A)	P-value
BMI (kg/m <sup>2</sup> )							
All	24.9 (24.2, 25.5)	26.2 (25.4, 27.1)	1.4 (0.14, 2.6)	0.02	27.2 (26.3, 28.2)	2.4 (1.0, 3.8)	0.00
MDI	25.1 (24.2, 25.9)	25.9 (24.8, 27.1)	0.9 (-0.9, 2.6)	0.72	27.0 (25.5, 28.4)	1.9 (-0.1, 4.0)	0.06
CSII	24.9 (23.9, 26.0)	27.2 (25.5, 28.8)	2.3 (-0.16, 4.7)	0.08	27.4 (25.5, 29.1)	2.5 (-0.2, 5.3)	0.08
From MDI to CSII	24.6 (23.5, 25.7)	25.6 (24.1, 27.1)	-1.0 (-1.2, 3.2)	0.82	27.3 (25.6, 29.1)	2.7 (0.2, 5.2)	0.03
Systolic BP (mmHg)							
All	137.0 (133.8, 140.3)	128.0 (124.7, 131.2)	-9.1 (-14.7, -3.5)	0.00	130.7 (128.1, 133.3)	-6.4 (-11.4, -1.3)	0.01
MDI	140.8 (136.1, 145.4)	131.7 (127.2, 136.3)	-9.1 (-17.0, -1.2)	0.02	131.6 (127.8, 135.3)	-9.2 (-16.4, -2.0)	0.01
CSII	138.5 (132.2, 144.8)	125.9 (119.5, 132.3)	-12.6 (-23.6, -1.7)	0.02	131.1 (126.1, 136.1)	-7.4 (-17.2, 2.4)	0.21
From MDI to CSII	131.8 (126.0, 137.7)	126.3 (120.6, 132.1)	-5.5 (-15.5, 4.5)	0.55	129.4 (124.8, 134.0)	-2.5 (-11.5, 6.6)	1.00
HbA1c (mmol/mol)							
All	8.0 (7.6, 8.3)	7.6 (7.4, 7.8)	-0.37 (-0.85, 0.10)	0.19	7.5 (7.3, 7.6)	-0.47 (-0.93, 0.00)	0.05
MDI	7.6 (7.1, 8.1)	7.6 (7.3, 7.9)	-0.02 (-0.70, -0.66)	1.00	7.4 (7.1, 7.6)	-0.25 (-0.91, 0.42)	1.00
CSII	8.3 (7.7, 9.0)	7.6 (7.2, 7.9)	-0.78 (-1.71, 0.14)	0.13	7.6 (7.2, 7.9)	-0.79 (-1.70, 0.12)	0.11
From MDI to CSII	8.0 (7.3, 8.6)	7.6 (7.3, 8.0)	-0.31 (-1.16, 0.54)	1.00	7.6 (7.3, 7.9)	-0.37 (-1.20, 0.47)	0.87
Total cholesterol (mmol/L)							
All	4.8 (4.7, 5.0)	4.5 (4.3, 4.7)	-0.32 (-0.62, -0.01)	0.04	4.9 (4.7, 5.0)	0.04 (-0.25, 0.32)	1.00
MDI	4.9 (4.6, 5.2)	4.6 (4.4, 4.9)	-0.27 (-0.70, 0.15)	0.38	4.9 (3.1, 6.7)	-0.01 (-0.4, 0.4)	1.00
CSII	5.1 (4.8, 5.4)	4.7 (4.3, 5.0)	-0.42 (-1.00, 0.17)	0.26	4.8 (2.4, 7.2)	-0.31 (-0.9, 0.24)	1.00
From MDI to CSII	4.5 (4.2, 4.8)	4.2 (3.9, 4.5)	-0.26 (-0.79, 0.29)	0.77	4.9 (4.6, 5.2)	0.42 (-0.1, 0.93)	0.15
eGFR (MDRD; mL/min per 1.73 m <sup>2</sup> )							
All	88.3 (85.3, 91.3)	83.3 (80.9, 85.8)	-4.9 (-9.7, -0.2)	0.37	92.0 (87.9, 96.1)	-3.7 (-2.5, -9.9)	0.44
MDI	90.4 (86.6, 94.7)	83.9 (80.4, 87.4)	-6.5 (-13.2, 0.27)	0.65	91.0 (85.3, 96.7)	0.6 (-8.0, 9.4)	1.00
CSII	83.3 (77.5, 89.2)	80.6 (75.8, 85.4)	-2.7 (-11.9, 6.5)	1.00	92.8 (84.7, 100.8)	9.4 (-2.7, 21.6)	0.19
From MDI to CSII	91.1 (85.7, 96.5)	85.5 (81.0, 89.9)	-5.7 (-14.1, 2.8)	0.32	92.2 (84.9, 99.5)	1.1 (-9.9, 12.1)	1.00

Data are the mean (95%CI). Mean differences and *P*-values are based on linear mixed models. BMI: Body mass index; BP: Blood pressure; MDI: Multiple daily injections; CSII: Continuous subcutaneous insulin infusion.

presented in Table 3. In total, BMI increased (mean difference: 2.4 kg/m<sup>2</sup>, 95%CI: 1.0-3.8; *P* < 0.00) and systolic blood pressure decreased [-6.4 mmHg, 95%CI: -11.4-(-1.3); *P* = 0.01] during the follow-up period.

The BMI increased significantly in the group of patients who switched from MDI to CSII (2.7 kg/m<sup>2</sup>; 95%CI: 0.2-5.2; *P* = 0.03), and systolic blood pressure decreased exclusively among MDI users [-9.2 mmHg; 95%CI: -16.4-(-2.0); *P* = 0.01]. In 2010, no differences were observed between the various treatment categories (*i.e.*, MDI, CSII and from MDI to CSII) concerning clinical parameters at the end of the follow-up.

### Long term follow-up-HRQOL

The observed course of the summary scores for the SF-36 and the EuroQol are presented in Table 2. The mean values and estimated changes in HRQOL are presented in Table 4. In total, no changes in both SF-36 component scores were observed. At baseline, patients administered MDI displayed the highest MCS. The SF-36 subscales for physical functioning [-8.3, 95%CI: -14.9-(-1.7)], social functioning [-8.9, 95%CI: -16.3-(-1.6)], role limitations due to emotional problems [-15.0, 95%CI: -27.0-(-3.0)] and vitality [-10.0, 95%CI: -18.4-(-1.7)] decreased significantly over time among patients on MDI. In addition, the MCS and PCS for patients administered MDI were significantly lower in 2010 compared with 1995, with a mean difference of -9.8 [95%CI: -16.3-(-3.2)] and -8.6 [95%CI: -15.3-(-1.8)], respectively. The subscale vitality ( $\Delta$  = 12.0, *P* = 0.03) displayed a more significant

decrease over time among patients using MDI compared with patients who switched from MDI to CSII, and a greater decrease was observed with the subscale role limitations due to emotional problems in patients administered MDI compared with CSII ( $\Delta$  = 22.1, *P* < 0.01) and switchers ( $\Delta$  = 18.0, *P* = 0.02). MCS and PCS did not differ between the treatment groups.

The EuroQol-VAS decreased among all patients [-7.3; 95%CI: -11.4-(-3.3); *P* = 0.001]. For patients using CSII or MDI throughout the follow-up period, the EuroQol-VAS decreased throughout the follow-up period to -8.1 [95%CI: -14.0-(-2.3)] and -9.6 [95%CI: -17.5-(-1.7)], respectively.

None of the HRQOL component scores differed from baseline among the patients who switched from MDI to CSII throughout the study. No differences concerning HRQOL parameters were observed between the various treatment categories in 2010.

## DISCUSSION

This is the first study to describe the long-term natural course of HRQOL among patients with T1DM treated with different insulin treatment modalities. In general, no relevant HRQOL changes were observed after a follow-up of 15 years. Between the treatment modalities, no differences with respect to metabolic and HRQOL parameters were observed during follow-up.

The approximately stable HRQOL reported in the current study is somewhat surprising given the natural decrease in HRQOL in an unselected population after 5

**Table 4** Estimated changes in health-related quality of life during follow-up

HRQOL parameters	1995 (A) mean	2002 (B) mean	Mean difference (B-A)	P-value	2010 (C) mean	Mean difference (C-A)	P-value
SF-36							
MCS							
All	81.3 (78.9, 83.7)	78.3 (75.6, 81.0)	-3.0 (-7.4, 1.4)	0.31	77.1 (74.2, 80.0)	-4.2 (-8.7, 0.41)	0.09
MDI	86.8 (83.4, 90.3) <sup>a</sup>	80.4 (76.5, 84.3)	-6.5 (-12.8, -0.14)	0.04	77.1 (72.9, 81.2)	-9.8 (-16.3, -3.2)	0.01
CSII	78.0 (73.4, 82.6)	77.0 (71.8, 82.3)	-1.00 (-9.5, 7.5)	1.00	76.5 (70.9, 82.1)	-1.6 (-10.4, 7.3)	1.00
From MDI to CSII	79.0 (74.8, 83.3)	77.5 (72.7, 82.3)	-1.5 (-9.3, 6.3)	1.00	77.9 (72.7, 83.1)	-1.1 (-9.2, 7.0)	1.00
PCS							
All	84.1 (81.6, 86.5)	81.1 (78.4, 83.8)	-3.0 (-7.5, 1.4)	0.31	79.5 (76.5, 82.4)	-4.6 (-9.3, 0.07)	0.06
MDI	88.7 (85.1, 92.2)	84.3 (80.3, 88.2)	-4.4 (-10.9, 2.0)	0.29	80.1 (75.9, 84.3)	-8.6 (-15.3, -1.8)	0.01
CSII	81.5 (76.7, 86.2)	79.3 (74.2, 84.5)	-2.1 (-10.7, 6.5)	1.00	77.8 (72.0, 83.5)	-3.7 (-12.8, 5.4)	0.98
From MDI to CSII	82.1 (77.7, 86.5)	79.6 (74.8, 84.4)	-2.5 (-10.4, 5.4)	1.00	80.5 (75.2, 85.8)	-1.6 (-9.9, 6.8)	1.00
EuroQol							
EuroQol-5D							
All	0.94 (0.92, 0.95)	0.91 (0.89, 0.93)	-0.03 (-0.06, 0.01)	0.12	0.94 (0.92, 0.95)	0.00 (0.03, -0.03)	1.00
MDI	0.96 (0.93, 0.98)	0.92 (0.88, 0.95)	-0.4 (-0.9, 0.01)	0.12	0.96 (0.93, 0.98)	0.00 (0.04, -0.04)	1.00
CSII	0.93 (0.90, 0.97)	0.91 (0.87, 0.95)	0.3 (-0.9, 0.04)	0.98	0.93 (0.90, 0.97)	0.00 (0.06, -0.06)	1.00
From MDI to CSII	0.92 (0.89, 0.95)	0.90 (0.86, 0.94)	0.02 (-0.08, 0.04)	1.00	0.92 (0.89, 0.95)	0.00 (0.05, -0.05)	1.00
EuroQol-VAS							
All	83.6 (81.4, 85.9)	76.9 (74.4, 79.5)	-6.7 (-10.9, 2.5)	0.01	76.3 (73.8, 78.8)	-7.3 (-11.4, -3.3)	0.01
MDI	86.4 (83.1, 89.7)	78.3 (74.6, 82.0)	-8.1 (-14.1, -2.1)	0.01	78.3 (74.8, 81.8)	-8.1 (-14.0, -2.3)	0.01
CSII	82.9 (78.5, 87.2)	76.4 (71.4, 81.3)	-6.5 (-14.5, 1.6)	0.16	73.3 (68.5, 78.1)	-9.6 (-17.5, -1.7)	0.01
From MDI to CSII	81.6 (77.6, 85.6)	76.1 (71.5, 80.6)	-5.5 (-12.9, 1.9)	0.22	77.3 (73.0, 81.6)	-4.3 (-11.5, 2.9)	0.45

Data are the mean (95%CI). HRQOL: Health-related quality of life; MDI: Multiple daily injections; CSII: Continuous subcutaneous insulin infusion; MCS: Mental component summary; PCS: Physical component summary. Mean differences and *P*-values are based on linear mixed models. <sup>a</sup>*P* < 0.05 at that moment in time *vs* the MDI and from MDI to CSII treatment groups.

years of follow-up and the occurrence of macrovascular and microvascular complications, both of which are known to decrease HRQOL<sup>[16-18]</sup>. However, this finding can be explained in part by improved clinical and/or metabolic parameters and/or the low number of patients who completed follow-up until 2010<sup>[19]</sup>. Arguing against the latter explanation, no change in HRQOL was observed after 7 years of follow-up, with 71.5% of the study sample intact.

Regarding the impact of the therapy mode, a decrease in both component scores of the SF-36 and EuroQol-VAS was observed among patients using MDI. One potential explanation for this finding is the relatively high scores of these HRQOL parameters at baseline compared with patients on CSII. Although speculative, this observation can be attributed to a relative short diabetes duration<sup>[7]</sup>.

In a recent Cochrane review, CSII was preferred over MDI with respect to HRQOL<sup>[11]</sup>. In accordance with our study, the only study among T1DM adults that used the SF-36 questionnaire demonstrated a significant improvement of the general health and mental health subscale in the CSII group compared with stable values in the MDI group after 32 wk of follow-up<sup>[20]</sup>. The other SF-36 scales, including the component scales, remained unaltered.

In our current study the HRQOL does not differ between modes of therapy, but the patient can choose his or her mode of choice in daily practice to a larger extent. This observation could partially explain the differences found in randomised trials (in favour of the treatment mode under investigation, mainly CSII) and the absence of differences in daily practice.

Although in many cases inadequate metabolic control is the main indication to commence CSII, we did not observe any significant difference regarding HbA<sub>1c</sub> at the start of therapy, HbA<sub>1c</sub> at final follow-up or changes in HbA<sub>1c</sub> over time between patients on MDI and those switching to CSII. Therefore, we conclude that the switch to CSII was initiated in some of the patients for reasons other than poor metabolic control.

Our findings also demonstrate that it is possible in daily practice to maintain moderate to good control of clinical parameters in a T1DM population and even improve these parameters. The reasons for this improvement remain open for discussion. Organisation of care, stricter guidelines, more education, improved pump and pen systems and a more active role of patients themselves may be involved. No definite conclusions can be drawn to explain this finding because not all these data were recorded in this study.

Interpretations of the findings from our study are limited by various factors, including the magnitude of loss to follow-up during the 15-year study period. Therefore, the results of our study should be interpreted with caution, and generalisability may be limited. This rate of loss to follow-up can be partly explained by the relatively young age of our population and the accompanied high relocation rate, which is the reason for approximately half of the loss to follow-up. In addition, 12 patients, mostly woman, moved to a hospital nearby after the departure of one of the diabetologists from our centre. Our results are also limited by the lack of appropriate controls and the use of questionnaires that measure general HRQOL.

In a conclusion, no differences with respect to meta-

bolic and HRQOL parameters between the various treatment modalities were observed after 15 years of follow-up between patients using MDI or CSII or patients switching from MDI to CSII in a setting in which patients, to a large extent, choose the mode of therapy that best suits them.

## ACKNOWLEDGMENTS

The results of this study were orally presented during the 49<sup>th</sup> Annual Meeting of the European Association for the Study of Diabetes in Barcelona.

## COMMENTS

### Background

Patients with type 1 diabetes mellitus (T1DM) require lifelong daily administration of insulin in order to achieve metabolic control. Multiple daily injections (MDI) and continuous subcutaneous insulin infusion (CSII) are the most common forms of insulin administration. It is likely that T1DM and its therapy have impact on health-related quality of life (HRQOL). At the present, the influence of the mode of therapy (MDI or CSII) on long-term HRQOL and metabolic control is unknown.

### Research frontiers

As HRQOL and metabolic control are important outcomes of T1DM management the influence of mode of therapy (MDI or CSII) on both outcomes is of great importance.

### Innovations and breakthroughs

In T1DM, relevant deterioration of HRQOL and glycaemic control during the course of the disease have been reported. In contrast, there are also reports which found no association between duration of diabetes and scores on quality of life scales. The present study is the first to describe the long-term natural course of HRQOL among patients with T1DM. In addition, results of the study show no differences with respect to HRQOL and metabolic parameters between the various treatment modalities after 15 years of follow-up between patients using MDI, CSII or patient who switched from MDI to CSII.

### Applications

The results of this study show that HRQOL and metabolic control is stable among T1DM patients. In addition, there is no impact of the mode of insulin therapy on HRQOL. Therefore, the findings of this study supports clinical decision making.

### Terminology

CSII: continuous subcutaneous insulin infusion, insulin is administered continuously in the SC tissue using an externally placed pump. MDI: multiple daily injections, insulin is administered in the SC tissue using injections.

### Peer review

This is a very well done and written clinical 15 year follow-up study considers the evaluation of on long term metabolic control and health related quality of life in type 1 diabetes patients treated with various therapy modes.

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